risk of acute liver failure (ALF) with the use of troglitazone for the treatment of diabetes. The report is divided into topical areas related to varying aspects of the issue.

We estimated the background rate of acute liver failure in the general population to the about 1 case per million persons per year (person-years). Using case reports data supplemented by usage data from a large multislate managed care organization, we estimated the rate of ALF with troglitazone to be about 1 case per 1000 person-years (accounting for underreporting). From three postmarketing clinical studies, the incidence of ALF ranged from about 1,200 to 17,000 per million person-years. Survival analysis suggested that the cumulative risk of ALF with troglitazone increased with continuing use of the drug. The implications of this for a product intended to bee used for decades should not be overlooked.

Based on a number of different analyses, underreporting of ALF with troglitazone was extensive. This highlights the limitations of voluntary (spontaneous) reporting systems. It also illustrates the danger of using changes in reporting over time as a message of success of an intervention. Reporting naturally decreases quickly after the start of marketing so that one cannot cite a decline in number of case reports as evidence that a safety problem has been successfully managed.

Multiple labeling revisions and ''Dear Healthcare Professional'' letters recommending monthly liver enzyme monitoring did not improve the safety profile of troglitazone. Enzyme monitoring was not performed regularly or reliably even after the July 1998 relabeling. Analysis of case reports suggested that even had monitoring been performed, it probably would not have prevented many, or perhaps any, cases of troglitazone-induced ALF. The ''point of no return,'' that is, of irreversibility and inevitable progression to liver failure appeared to be reached within about a month or less of a time when liver enzymes were normal.

Troglitazone appeared to confer a substantially greater risk of ALF than rosiglitazone. However, the risk of ALF with rosiglitazone appeared to be higher than the expected background rate.

BACKGROUND ON ACUTE LIVER FAILURE

Acute liver failure is a rapidly progressive disorder characterized by hepatic encephalopathy, and frequently, coagulopathy (both platelets and clotting factors), methobilic derangements (lactic acidosis, hypoglycemia, electrolyte abnormalities), high output hypovolemic heart failure, renal failure and sepsis. Survival without transplant is below 25%.

Drug-induced ALF is usually more aggressive than viral forms, with survival rates around 10% without transplant. There are several competing classification systems for ALF, each relying on the length of time it takes for a patient to progress from initial symptoms (US) or jaundice (UK, France) to hepatic encephalopathy. The U.S. definition classifies ALF as progressive from initial symptoms of liver dysfunction to encephalopathy within 6 months. In Europe, progression from jaundice to encephalopathy within 12 weeks is classified as ALF. In subsequent work, we used the European criteria. We choose the latter criteria because their shorter time-window more closely reflected the fulminant nature of the cases we were receiving. Also, the onset of jaundice is a clearer and more definite time-point from which to begin counting compared with initial symptoms, the onset of which might be vague and hence unlikely to be reported accurately in case reports.

The etiology of ALF varies somewhat by country (slide 2). Until recently, about 70% of ALF in the U.S. was due to viral hepatitis (primarily hepatitis B), with 15% due to acetaminophen and about 10% due to other drugs and toxins.

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The Diabetes Prevention Program (DPP) was a NIH-sponsored clinical trial performed on patients with impaired glucose tolerance (IGT), but not diabetes. Its purpose was to study whether treatment of IGT with oral hypoglycemic agents could prevent or delay the onset of diabetes. One arm of the trial included 585 patients treated with troglitazone on average for one year. From this group, one patient died of fulminant ALF, for an incidence rate of 1,724 per 10^6 person-years (95% confidence interval 44–9,569).

The REACH study was a Warner-Lambert/Parke-Davis sponsored postmarketing study to collect additional information on efficacy and safety of troglitazone. At the time when 2,433 patients were enrolled in the study, with an average duration of treatment <4 months, one patient died of fulminant ALF, for an incidence rate of 1,274 per 10^6 person-years (95% CI 32–7,077).

Another Warner-Lambert/Parke-Davis postmarketing study, Protocol II, was conducted to study the effect of troglitazone use on the insulin does required by diabetic patients enrolled in the study. There were 233 patients enrolled in this randomized double-blind placebo-controlled trial, each treated for a maximum of 6 months. Of this group, one died of liver failure. Of note, this patient developed liver enzyme abnormalities in November 1998 and was withdrawn from the study. His liver enzymes did not normalize and in early March 1999, the blind was broken for this patient to see whether he had received troglitazone or placebo. He had been treated with troglitazone. He was in hospital for evaluation of his liver disease on the day of the March 1999 advisory meeting, and died of liver failure three days after the meeting. Assuming that 50% of randomized patients were treated with troglitazone for a maximum of 6 months, the incidence rate in this study was about 16,949 per 10^6 person-years (95% CI 429–90,855).

In each of these three studies, fatal liver failure was observed at an extremely high rate, ranging from 1,274 to 16,949 per 10^6 person-years. Based on data from the published literature discussed above, we would expect about 1 case of ALF per 10^6 person-years meaning that the occurrence of liver failure in these studies was from about 1,300/ to 17,000/times greater than would be expected by chance.

In the original troglitazone NDA, there were 2 cases of jaundice/hepatitis (one of which was hospitalized) and 1 other patient hospitalized with drug-induced hepatitis, but no cases meeting our definition of ALF. This finding is still compatible with an ALF incidence rate of 2,584 per 10^6 person-years.

These studies demonstrate that liver enzyme monitoring on a monthly basis does not prevent the occurrence of ALF with troglitazone. Furthermore, they collectively support the conclusion that the underlying incidence rate of ALF due to troglitazone is extremely high, probably in the range of 1,000 to 2,000 per 10^6 person-years, representing about a 1,000- to 2,000-fold increase in liver failure risk. Another way of stating this is that 1–2 out of every 1,000 patients (1/500=–1/1,000) who use troglitazone for one year will die of ALF.

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DISCUSSION

The data presented here provide a comprehensive picture of liver failure risk with troglitazone. Premarketing clinical trial data from the company's NDA for troglitazone showed that ALT elevation above 3 ULN occurred in 1.9% of treated patients. More importantly, it provided an estimate of the incidence of hospitalized drug-induced hepatitis that was more than 50-fold greater than the background rate suggested by the literature.

Soon after US marketing began, FDA began receiving case reports of ALF in patients who were using troglitazone. A series of labeling revisions and ''Dear Healthcare Professional'' letters followed, recommending increasing performance of liver enzyme monitoring as a means of reducing or eliminating risk of ALF. Despite those interventions, cases continued to be steadily reported to FDA.

Our analyses of the original 43 US cases found that there were no apparent risk factors by which to identify patients who might be at increased risk of developing ALF while using troglitazone. Furthermore, the onset of liver disease was usually heralded by the appearance of jaundice, by which time, irreversibility had been passed in these cases who usually progressed quickly to encephalopathy: Examination of 12 cases with adequate liver enzyme monitoring prior to onset of liver disease showed that in 75%, patients went from having normal liver enzymes to irreversible progression towards liver failure within the recommended monitoring interval. In the three other cases, the patients remained on troglitazone after the first recorded enzyme abnormally so that it was not possible to identify when the point of irreversibility was passed. Of note, there were no differences between the 12 ''rapid risers'' and the remaining 31 cases for whom we lacked data on the time-course of their liver enzyme elevations. From these data, we concluded that it was not possible to prevent ALF by patient selection or to predict who was at risk. Also, monthly liver enzyme monitoring would probably fail to prevent at least 75% and perhaps 100% of cases.

The cases reported to FDA were also used to estimate the pattern of ALF risk over time of continued use of troglitazone. This too was presented at the March 1999 advisory meeting. Analysis showed a marked rise in risk beginning with the first month of troglitazone use. With continued follow-up after the advisory meeting, our expectation was confirmed that heightened ALF risk continued for as long as troglitazone was used. In other words, the risk of ALF did not disappear after the first few months or even first 18 months of use. The pattern suggested that cumulative risk of ALF would continue to rise for as long as troglitazone was used, having important implications for a drug intended to be used for 20, 30 or 40 years or longer.

Against this backdrop of case reports, epidemiologic data suggested that the expected incidence rate of ALF in the general population was about 1 case per million per year. The data from case reports were markedly higher than this. At the March 1999 advisory meeting, we presented data showing that if we assumed there was no underreporting, the cumulative risk of ALF was about 1 case per 15,000 patients who used troglitazone for at least 8 months. If we factored into the analysis that only 10% of cases had been reported, the cumulative risk became 1 case per 1,500 at 8 months (about 1 case per 1,000 per year). With an additional year's worth of case reports (through December 1999), the cumulative risk was 1 case per 7,000 patients after 18 months of troglitazone use, assuming no underreporting. With 10% reporting, this would be 1 case per 700 patients at 18 months (about 1 case per 1000 per year). The first analysis through 8 months of use led us to conclude prior to the March 1999 advisory meeting that the risk of ALF with